REMARKS

Claims 23-30 and 32-46 were pending in the present application. Claims 23-25, 27-30, 32-34 and 36-46 are rejected and claims 26, 35, and 41 are objected to. By virtue of this response, claims 27, 37, and 41 have been amended, no claims have been cancelled, and no new claims have been added. Accordingly, claims 23-30 and 32-46 are currently under consideration. Allowance of the pending claims is respectfully requested.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and, moreover, have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Claim Amendments

The amendments to claims 27, 37, and 41 are fully supported by the original application. No new matter has been added by the amendments to the claims.

Minor amendments to claim 27 has been amended to more clearly state the claimed invention. The claim, as amended, more clearly indicates the characteristics of the composition itself which are dictated by the composition's intended use. Support for this amendment is found throughout the application as originally filed.

Claims 37 and 41 have been corrected by amendment to refer to claim 33 instead of claim 23. Support is found throughout the application as filed.

Claim objections under 35 C.F.R. § 1.75

Claim 41 was objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 24. By virtue of this amendment, claim 41 has been amended to refer to claim 33, rather than claim 23. Applicants respectfully request that the objection to claim 41 be withdrawn.

Claim Rejections under 35 U.S.C. § 112

1. Claim 37 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In response, Applicants have amended claim 37 to more properly refer to claim 33, rather than claim 23. Applicants respectfully request that the rejection to claim 37 under 35 U.S.C. § 112 be withdrawn.

2. The Applicants would like to thank the Examiner for withdrawing the rejection of Claim 32 under 35 U.S.C. § 112, first paragraph.

Information on HLA-Haploidentity

Each of the pending claims in the present application relates to HLA-haploidentical antigen-presenting cells, or their generation or use. Information regarding the meaning of HLA-haploidentity is found in the specification, e.g., at page 6, line 32, to page 7, line 24. Chromosome 6 is the chromosome that carries the HLA gene complex (HLA-A, B, C, DR, DQ and DP alleles, among others). In order for antigen-presenting cells to be HLA-haploidentical to those of a patient, the donor of the antigen-presenting cells and the patient must be related and must have both inherited the same HLA gene complex on one of their copies of chromosome 6, but not on their other copy of chromosome 6. As a result, all of the alleles of the HLA gene complex on one of the two copies of chromosome 6 of the HLA-haploidentical antigen-presenting cell will generally be identical to those of the patient.

"HLA-matched" cells are not equivalent to "HLA-haploidentical" cells. The HLA gene region of each copy of chromosome 6 contains many hundreds of genes. The matching of 3 or 6 of the HLA alleles on one copy of chromosome 6 between a donor and the patient does not establish HLA-haploidentity since the donor and patient may not be related and HLA-haplotypes can still be mismatched for hundreds of other polymorphic alleles on that same chromosome copy containing the matched HLA alleles.

The following non-limiting, hypothetical example of the inheritance of HLA-haplotypes is provided to further help illustrate the nature of HLA-haploidentical individuals (and their cells) for the Examiner.

Father	Mother
HLA: A/B	HLA-C/D

Child 1	Child 2	Child 3	Child 4	(Child 5)
A/C	A/D	B/C	B/D	B/D

In the hypothetical example of a family diagrammed above, each individual has two copies of chromosome 6 which carries the HLA gene complex. Each chromosome/HLA gene complex is referred to as an HLA-haplotype. Because of the very high polymorphism in the various loci of an HLA-haplotype, two unrelated individuals, like the father and the mother in a typical family, will have two different HLA-haplotypes (A/B versus C/D) and will therefore be HLA-disparate.

According to the rules of genetic inheritance of Mendel, each child inherits one copy of chromosome 6 (and thereby one HLA-haplotype) from each parent. This means that the parental HLA-haplotypes can segregate in the children in four different combinations: A/C, A/D, B/C, and B/D. If there are many children in a family some children will inherit the same combination of HLA-haplotypes, as shown in this example for child 4 and child 5. These two children are HLA-identical to each other (not HLA-haploidentical) since both of their HLA-haplotypes are genetically identical; they are derived by genetic descent from the same parents.

According to the terminology of the experts in the field of HLA-immunogenetics and transplantation biology and medicine, the relationships of the family members in the example of a family diagrammed above are as follows:

Father and Mother: HLA-disparate. They each have two HLA-haplotypes that are different and unrelated to each other, i.e. A/B versus C/D. (This can also be referred to as fully HLA-mismatched).

Child 4 and Child 5: HLA-identical. These children each inherited the HLA-haplotype B from the father and HLA-haplotype D from the mother. They are therefore both HLA-B/D and have two identical HLA-haplotypes that are genetically identical by descent from the same parents. They are therefore HLA-identical to each other.

Father and Children 1-5: HLA-haploidentical. Each of the children 1-5 have one HLA-haplotype in common (i.e. A or B) with and one HLA-haplotype that is different (i.e. C or D) from their father. They are HLA-haploidentical. Since only one HLA chromosome is shared this is a haploid sharing (in contrast to diploid sharing when both chromosomes are identical as in children 4 and 5).

Mother and Children 1-5: HLA-haploidentical. Each of the children have one HLA-haplotype in common (i.e. C or D) with and one HLA-haplotype that is different (i.e. A or B) from their mother. They are therefore HLA-haploidentical. Since only one HLA chromosome is shared this is a haploid sharing (in contrast to diploid sharing when both chromosomes are identical as in children 4 and 5).

Child 1 and Child 2: HLA-haploidentical. These children share one genetically identical HLA-haplotype and differ in one HLA-haplotype. They are HLA-haploidentical to each other.

Child 1 and Child 3: HLA-haploidentical. These children share one genetically identical HLA-haplotype and differ in one HLA-haplotype. They are HLA-haploidentical to each other.

Child 2 and Child 4: HLA-haploidentical. These children share one genetically identical HLA-haplotype and differ in one HLA-haplotype. They are HLA-haploidentical to each other.

Child 3 and Child 4: HLA-haploidentical. These children share one genetically identical HLA-haplotype and differ in one HLA-haplotype. They are HLA-haploidentical to each other.

Child 1 and Child 4: HLA-disparate. These two children differ genetically for both HLA-haplotypes. They are fully HLA-mismatched and therefore are HLA-disparate.

Child 2 and Child 3: HLA-disparate. These two children differ genetically for both HLA-haplotypes. They are fully HLA-mismatched and therefore are HLA-disparate.

Claim rejection under 35 U.S.C. § 102(b)

Claims 27-30 and 43 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Kugler et al. (Nature Medicine, 2000, Vol. 6, pp. 332-336). Applicants respectfully traverse this rejection.

Claim 27, as amended, is directed to a pharmaceutical composition, comprising antigen-presenting cells into which proteins and/or peptides, or RNA or DNA or cDNA encoding said proteins and/or peptides, which are overexpressed in tumor cells of a patient with a tumor disease or are derived from tumor cells from the patient, have been introduced, wherein the antigen-presenting cells are HLA-haploidentical with respect to those of the patient. Claims 28-30 and 43 are directed to certain pharmaceutical compositions of claim 27.

To anticipate a claim, a reference must teach or suggest each and every element of the claim. The Kugler et al. reference does not anticipate claim 27 (or its dependent claims 28-30 and 43), because the Kugler et al. reference does not teach or suggest each and every element of claim 27. The Kugler et al. reference describes a vaccine that is made by fusing tumor cells from a patient with dendritic cells from an unrelated donor to generate a hybrid cell. This hybrid cell would at least initially necessarily be a tetraploid cell comprising both of the two HLA-haplotypes from the tumor cells, as well as both of the two HLA-haplotypes from the dendritic cells. The hybrid cell that is described in the Kugler et al. reference is not HLA-haploidentical to the patient from which

the tumor cells were obtained (because both HLA haplotypes from the patient are present in the hybrid cell), is not HLA-haploidentical to the donor of the dendritic cells (because both HLA haplotypes from the donor are present in the hybrid cell), and is also not necessarily HLA-haploidentical to anyone else with a tumor disease, since that person with the tumor disease would have to be a relative that has inherited the same HLA gene complex on one copy of chromosome six as on one copy of chromosome six in the hybrid cell.

The Examiner has stated that the hybrid cell described in the Kugler et al. reference "remains inherently HLA haploidentical to an individual which is HLA haploidentical to the donor of the dendritic cells used by Kugler et al." Even if that were correct, the cell would still not necessarily be HLA-haploidentical to any individual with that tumor disease. Inherent anticipation requires that the inherent characteristics in question must necessarily be present in the disclosures of the prior art. See MPEP § 2112(IV). This is not the case with the cells in Kugler et al. Accordingly, claim 27 (and dependent claims) are not inherently anticipated by the Kugler et al. reference.

Since the Kugler et al. reference does not teach or suggest each and every element of claims 27-30 and 43, Applicants respectfully request that the rejection of claims 27-30 and 43 under 35 U.S.C. § 102(b) be withdrawn.

Claim Rejections under 35 U.S.C. § 103(a)

1. Claims 23, 27, 28, 30, 31, 32, 40 and 43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Greenman et al. (WO 99/03976). Applicants respectfully traverse this rejection.

Claim 23 is directed to a method for the generation of HLA-haploidentical antigen-presenting cells for the treatment of tumor diseases in a patient. The method comprises providing antigen-presenting cells from a donor which are HLA-haploidentical with respect to those of the patient and introducing proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived from autologous tumor cells

into the HLA-haploidentical antigen-presenting cells. Claim 27, as amended, is directed to a pharmaceutical composition, comprising antigen-presenting cells into which proteins and/or peptides, or RNA or DNA or cDNA encoding said proteins and/or peptides, which are overexpressed in tumor cells of a patient with a tumor disease or are derived from tumor cells from the patient, have been introduced, wherein the antigen-presenting cells are HLA-haploidentical with respect to those of the patient. Claims 28, 30, 32, and 43 are directed to certain pharmaceutical compositions of claim 27. Claim 31 was previously cancelled. Claim 40 is directed to the method of claim 23 characterized in that the antigen-presenting cells are dendritic cells.

To establish a prima facie case of obviousness, the prior art references must teach or suggest each and every claim limitations. The Greenman et al. reference does not render claims 23 and 27, nor the rejected dependent claims, obvious because it does not teach or suggest all claim limitations. For instance, the Greenman et al. reference does not teach or suggest the generation of antigen-presenting cells (into which the specified proteins, peptides, RNA, DNA, and/or cDNA have been introduced) that are *HLA-haploidentical* with respect to those of an intended patient having the tumor disease.

The Greenman et al. reference describes a procedure for blocking the proliferation of isolated leukocytes from a donor so that the cells will not expand in a recipient and cause graft-versus-host-disease (GVHD) when the cells are used in a Donor Leukocyte Infusion (DLI) treatment, but will still retain their function to combat tumor cells or pathogen-infected cells in the recipient following bone marrow transplantation (BMT). The reference further indicates that, in some cases, donor antigen-presenting cells which have been pulsed with an antigen or co-cultured with a diseased cell can be exposed to the donor leukocytes to stimulate the T-cells prior to infusion of the donor leukocytes in a recipient. As noted by the Examiner, the Greenman et al. reference does not teach or suggest the administration of the antigen-presenting cells to the recipient, only administration of the leukocytes.

Contrary to the assertions of the Examiner, the Greenman et al. reference makes clear that the leukocyte donor (and therefore any antigen-presenting cells from that same donor) must be

allogeneic with respect to the intended recipient (see, e.g., lines 20-21 of page 26). Although the reference suggests that the allogeneic donor, may, in some instances, be HLA-matched to the recipient at certain HLA-loci, even HLA-matched persons matched in three of the six HLA loci of HLA-A, B, and DR, are not necessarily "HLA-haploidentical" as the term is used in the art and in Applicant's specification. An unrelated donor, even if HLA-matched, cannot be HLA-haploidentical to the recipient, since the donor and recipient do not share an HLA chromosome that is generally identical at all HLA loci and that has been obtained by genetic descent. Rather, an unrelated, HLA-matched HLA donor is selected for sharing some much more limited number of alleles of the HLA gene complex with the patient. The HLA gene region contains many hundreds of genes and the selection for 3 to 6 allele matches does not equal HLA-haploidentity, since without further matching for all of the genes in the complex on one chromosome, the HLA-haplotypes will still be mismatched for hundreds of other polymorphic alleles. HLA-haploidentical chromosomes are only present in individuals who are family members. Regardless of whether the Greenman et al. reference "provides preferred embodiments for less than a complete match in cases where the patient lacks a HLA-identical donor" as proffered by the Examiner, the Examiner has identified no rationale as to why it would be obvious to seek a donor that is essentially identical to the recipient with respect to each of the hundreds of polymorphic HLA alleles on one of the two copies of chromosome 6, a relationship that can only be achieved with a close relative who inherited an identical HLA-haplotype, and to combine that very specific particular approach, when countless other allogeneic cell possibilities would be available, with the *in vitro* stimulation of the donor leukocytes with antigen-presenting cells(APCs).

Furthermore, contrary to the assertions of the Examiner, the Greenman et al. reference actually teaches away from the use of donors who share too much genetic identity with the recipient, and therefore teaches away from the use of HLA-haploidentical donors. For instance, the Greenman et al. reference states at page 3, lines 18-27,

> The eradication of disease after DLI is thought to be due to an immune reaction of the graft against the tumor cells, i.e., GVL effect (Barrett, J. *et al., Cur. Op. Onc.* 8:89-95, 1996)....An immune response is necessary for the effect to occur which has been

> experimentally demonstrated by the higher rates of relapse following syngeneic BMTs as compared to allogeneic BMTs (Duell, T., Ann. Int. Med. 126:184-192, 1997). In Japan, the high homogeneity of the population has resulted in ineffective DLA therapy since the random donors and hosts are not sufficiently allogeneic (Takahashi, K. *et al.*, Lancet, 343:700-702, 1994).

Thus, the Greenman et al. reference teaches that it is undesirable to have the donor and recipient have as many matching HLA alleles in common as an unrelated, but perhaps at least partially HLA-matched, donor in Japan would have with a recipient in Japan, a country with a high degree of genetic homogeneity among the population. Such a closely genetically related donor as an HLA-haploidentical parent, child, or sibling would generally be expected to have an even greater degree of genetic identity with the recipient than an unrelated, HLA-matched Japanese donor would have with a recipient. Accordingly, when the Greenman et al. reference teaches away from the use of donors having as much genetic identity to the recipients as unrelated Japanese pairs would have, the reference also teaches away from the use of HLA-haploidentical donors. The Greenman et al. reference does not, therefore, render the claims obvious.

The use of HLA-haploidentical APCs from closely related donors in the vaccines provides advantages over the use of allogeneic cells that are not HLA-haploidentical, even if those allogeneic cells are "HLA-matched." These advantages were neither taught nor suggested by the prior art. Applicants contend that HLA-haploidentical cells will generally provide the proper balance between providing enough MHC class I and class II matches for adaptive immunity to develop and enough mismatches for stimulating the innate immunity. This balance is superior to that which may be provided by allogeneic cells that are not HLA-haploidentical.

In light of the above remarks regarding the nonobviousness of claims 23, 27, 28, 30, 32, 40 and 43 over the Greenman et al. reference, Applicants respectfully request that the rejection of claims 23, 27, 28, 30, 32, 40 and 43 under 35 U.S.C. § 103(a) be withdrawn.

2. Claims 23, 25, 27, 28, 30, 31, 32, 33, 34, 38, 39, 40, 43, 44 and 45 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Greenman et al. (WO 99/03976) in view of Nair et al. (WO 97/41210). Applicants respectfully traverse this rejection.

Independent claims 23 and 27 are as indicated above. Claims 28, 30, 32, and 43 are directed to certain pharmaceutical compositions of claim 27. Claim 31 was previously cancelled. Dependent claims 25, 38, 39, 40, and 45 are directed to certain methods of claim 23. Independent claim 33 is directed to a method of treatment of tumor diseases in a patient comprising administering to said patient a therapeutically effective amount of HLA-haploidentical antigen-presenting cells into which proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived from autologous tumor cells have been introduced. Dependent claims 34 and 44 are directed to certain methods of claim 33.

Just as the Greenman et al. reference fails to teach each and every element of the claims, the combination of Nair et al. with Greenman et al. likewise fails to teach each and every element of the rejected claims. The cited references, both alone and in combination, simply fail to teach or disclose the generation or use of antigen-presenting cells that are *HLA-haploidentical* to the patient with the tumor disease. As described above with respect to the rejection under 35 U.S.C. § 103(a) over Greenman et al., the Greenman et al. reference teaches the generation and administration of an allogeneic therapeutic leukocyte composition and, in some cases, the use of allogeneic antigen-presenting cells to stimulate the T-cells of the leukocyte composition *in vitro*. The Greenman et al. reference teaches away from using donors that are too similar with respect to the HLA-haplotype genes. The Nair et al. reference, on the other hand, teaches the administration of autologous or HLA-matched APCs, but again, does not teach or suggest the use of HLA-haploidentical APCs which would have full HLA-identity on one of the two HLA-haplotype chromosomes with a related patient having the tumor disease.

In light of the above remarks regarding the nonobviousness of claims 23, 25, 27, 28, 30, 31, 32, 33, 34, 38, 39, 40, 43, 44 and 45 over the Greenman et al. reference in view of the Nair et al.

reference, Applicants respectfully request that the rejection of claims 23, 25, 27, 28, 30, 31, 32, 33, 34, 38, 39, 40, 43, 44 and 45 under 35 U.S.C. § 103(a) be withdrawn.

3. Claims 23-25, 27-30, 32-34, 37-46 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Greenman et al. and Nair et al. and further in view of Storkus et al. (US Patent No. 6,077,619). Applicants respectfully traverse this rejection.

Independent claims 23, 27, and 33 are as indicated above. Dependent claims 28, 29, 30, 32, and 43 are directed to certain pharmaceutical compositions of claim 27. Dependent claims 24, 25, 26, 38, 39, 40, 45, and 46 are directed to certain methods of claim 23. Dependent claims 34, 37, 41, 42, and 44, as amended, are directed to certain methods of claim 33.

Just as the combination of the Greenman et al. reference and the Nair et al. reference fails to teach each and every element of the rejected claims, the combination of the Greenman et al., Nair et al., and Storkus et al. references likewise fails to teach each and every element of the rejected claims. As explained above with respect to the rejections under 35 U.S.C. § 103(a) over the Greenman et al. and/or Nair et al. references, these two references, alone or in combination, fail to suggest or teach all elements of the independent claims 23, 27, and 33 and, therefore, their dependent claims. The Examiner has not provided any reasoning as to why the addition of the teachings of Storkus et al. would compensate for the shortcomings of the Greenman et al. and Nair et al. references in providing all elements of the rejected independent claims. Accordingly, the Examiner has not properly established prima facie obviousness.

In light of the above remarks regarding the nonobviousness of claims 23-25, 27-30, 32-34, 37-46 over the Greenman et al. reference in view of the Nair et al. reference and further in view of Storkus et al., Applicants respectfully request that the rejection of claims 23-25, 27-30, 32-34, 37-46 under 35 U.S.C. § 103(a) be withdrawn.

Claims allowable if rewritten in independent form

Claims 26 and 35 have been objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants wish to thank the Examiner for indicating the allowability of these claims if rewritten. As indicated above, however, Applicants contend that the rejection of base claims 23 and 33 should be withdrawn. Accordingly, Applicants respectfully request that the objections to claims 26 and 35 be withdrawn.

Double Patenting

The Applicants would like to thank the Examiner for withdrawing the provisional rejection of claims 23-42 under 35 U.S.C. § 101 over U.S. Serial No. 10/663,421.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 559412000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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